Articles

Prevalence and Reversibility of the Hepatopulmonary Syndrome After Liver Transplantation

The Cleveland Clinic Experience

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To ascertain the prevalence and reversibility of the hepatopulmonary syndrome, we reviewed the cases of 98 patients undergoing liver transplantation at the Cleveland (Ohio) Clinic Foundation from June 1988 through July 1992 and identified 4 patients with clinically recognized hepatopulmonary syndrome (prevalence 4%). All 4 patients ultimately had complete reversal of their disorder. As reviewed herein, the prevalence of the hepatopulmonary syndrome in the current series is lower than in previous reports, possibly reflecting a dependence on its clinical recognition in this series rather than the use of routine screening tests. This report confirms previous experience that the hepatopulmonary syndrome may be reversible after transplantation.

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The hepatopulmonary syndrome is characterized by a triad of impaired arterial oxygenation, hepatic dysfunction, and the presence of intrapulmonary vascular dilatations.[1-5] Clinical features include dyspnea, orthodeoxia, tachypnea, cyanosis, and digital clubbing.

Despite earlier impressions that the hepatopulmonary syndrome is irreversible and that it is a contraindication to liver transplantation (because posttransplantation hypoxemia could exacerbate graft failure),[3,6-9] recent observations suggest that the syndrome can resolve after liver transplantation.[10-20] In the context that the pathogenesis of the hepatopulmonary syndrome remains unknown, however, predicting reversal after liver transplantation currently remains impossible.

This study was undertaken to assess the frequency and time course of the reversal of the hepatopulmonary syndrome following liver transplantation. Because overall estimates of the prevalence of the syndrome vary widely, another goal of this research was to examine its prevalence among liver transplantation candidates referred to the Cleveland (Ohio) Clinic Foundation.

Patients and Methods

To identify patients with the hepatopulmonary syndrome before undergoing liver transplantation and also the group in whom posttransplantation reversibility could be assessed, we reviewed retrospectively the roster of all patients undergoing liver transplantation at the Cleveland Clinic Foundation from June 1988 through July 1992. Over this 49-month period, 98 patients underwent liver transplantation at our institution. The subjects of the current report are the 4 patients in whom the hepatopulmonary syndrome was suspected (and subsequently confirmed) by their managing physicians. Although routine screening for the syndrome—by the physiologic assessment of shunt fraction, by imaging using technetium Tc 99m-labeled macroaggregated albumin or contrast-enhanced echocardiography, or both—was not part of our routine pretransplantation evaluation protocol until after the current study was completed (November 1993), our previously reported experience with a patient whose hepatopulmonary syndrome and associated digital clubbing reversed after liver transplantation heightened our suspicion for the syndrome.[11]

The following criteria were used for diagnosing the hepatopulmonary syndrome in this series:

- Impaired oxygenation, defined as an elevated alveolar-arterial oxygen gradient ($P_{AO_2} - P_{aO_2}$) for age (using a maximal normal age-specific value of $P_{AO_2} - P_{aO_2}$ as age $\div 4 + 4$);
- The presence of chronic liver dysfunction; and
- Evidence of a right-to-left shunt, based on the results of radionuclide scans using ^{99m}Tc-macroaggregated albumin, contrast-enhanced echocardiography, or both.

Radionuclide scans using ^{99m}Tc-macroaggregated albumin were done using standard techniques.[21] Specifically, after the administration of 4 mCi of ^{99m}Tc-macroaggregated albumin (mean particle diameter, 20 to 50 μm), scans were taken over the kidney and brain to detect particles bypassing the pulmonary capillaries (the smaller diameter [8 to 15 μm] of which would trap the

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macroaggregated albumin particles). The appearance of radionuclide in the brain, kidneys, or both denotes the qualitative presence of a right-to-left shunt.

Contrast-enhanced surface echocardiography was performed using standard echocardiographic techniques (Sonos-1000, HP-77020A, Hewlett Packard, Andover, Massachusetts). Contrast consisted of microbubbles (60 to 90 μm) created by administering a hand-agitated saline solution or indocyanin intravenously. The appearance of microbubbles or contrast in the left atrium or the left ventricle (or both) three to six cardiac cycles after their appearance in the right atrium denotes an intrapulmonary right-to-left shunt.[22,23] Transesophageal echocardiography was not routinely performed.[24] As previously reported, one of the four patients underwent pulmonary angiography and was found to have a type 1 angiographic pattern (diffuse, "spongy" vascularity).[11,25]

Other tests included arterial blood gas measurements, both while the patient was breathing room air (either standing or supine as indicated) or after the patient had breathed 100% oxygen. The shunt fraction was determined by obtaining an arterial blood specimen after the patient breathed 100% oxygen through a tight-fitting face mask for at least 20 minutes. The shunt fraction was calculated according to a published nomogram that assumes an arteriovenous oxygen content difference of 5 mg per dl.[26]

Orthodeoxia was defined as a decline in room-air arterial oxygen tension of 10 mm of mercury or more when the patient was standing (versus the baseline seated or supine value). The room-air $P_{AO_2} - P_{aO_2}$ gradient was calculated according to a standard formula using a respiratory quotient value of 0.8. Age-specific normal values were calculated using the formula age ÷ 4 + 4.[27]

Static pulmonary function tests included spirometry and the measurement of lung volumes and steady-state diffusing capacity. This spirometry was done using a pneumotachygraph-based spirometer (Model TL, Spinnaker, and Excel, Cybermedic, Inc, Boulder, Colorado) without inhaled bronchodilators. We recorded the highest spirometric values based on three acceptable spirometry maneuvers, as defined by American Thoracic Society criteria.[28] Predicted values for the forced expiratory volume in 1 second and the forced vital capacity were based on published predictive equations.[29] Lung volumes were determined by helium dilution using published predictive equations.[30] With the patient seated, the lungs' diffusing capacity for carbon monoxide was measured using a single-breath technique and comparing with predicted normal values.[31]

Results

Of 98 cases of liver transplantation reviewed, 4 patients were suspected clinically by their managing physicians of having the hepatopulmonary syndrome. In each patient, further pretransplantation evaluation confirmed the presence of the syndrome, yielding a prevalence of clinically suspected hepatopulmonary syndrome of 4% (4/98) in this series. Patient 1 was the subject of an earlier report from our group.[11]

Characteristics of these four patients with the hepatopulmonary syndrome who subsequently underwent liver transplantation are summarized in Table 1. Their mean age was 33.5 years (range, 5 to 52). All patients had limited exercise tolerance and digital clubbing. Cutaneous spider angiomata were noted in three patients. Orthodeoxia was present in one of the two patients for whom matched supine and standing room-air arterial blood gas values were available.

The pretransplantation physiologic features of these four patients are summarized in Table 2. Among the three patients with available measurements of diffusing capacity, values were uniformly low (mean, 51.6% predicted; range, 34% to 64% of predicted). Similarly, among the three patients with available room-air arterial blood gas values, the $P_{AO_2} - P_{aO_2}$ gradients were elevated in all three (mean value, 58.1 mm of mercury; range, 43 to 66 mm of mercury). In the fourth patient, the pretransplantation P_{aO_2} with the patient receiving 6 liters of transtracheal oxygen was 45 mm of mercury. The mean pretransplantation shunt fraction was 18.7% in the three patients studied (range, 18% to 20%).

As shown in Figure 1, the hepatopulmonary syndrome resolved in all four patients following liver transplantation. The reversal of the right-to-left shunt was demonstrated by a return to normal shunt fraction measurements in three patients following liver transplantation and, in patient 2, who was 5 years old, by less invasive contrast-enhanced echocardiography. The mean posttransplantation shunt fraction was 4.5% (range, 3.5% to 5.1%). The interval over which the hepatopulmonary syndrome was

TABLE 1.—*Characteristics of Patients With the Hepatopulmonary Syndrome Undergoing Liver Transplantation*

Patient	Age at Transplantation	Sex	Diagnosis	Digital Clubbing	Orthodeoxia*	Transplantation Date
1.....	38	F	Primary biliary cirrhosis	Yes	No	6/12/88
2.....	5	F	Postnecrotic cirrhosis	Yes	NA	7/20/90
3.....	52	M	Laennec's cirrhosis	Yes	NA	6/28/91
4.....	39	F	Autoimmune chronic active hepatitis	Yes	Yes	7/29/92

NA = data not available

*Orthodeoxia is defined as a decline in the P_{aO_2} value with the patient breathing room air of 10 mm of mercury from supine to standing.

TABLE 2.—*Pretransplantation Physiologic Measurements*

Patient	FEV_1, % Predicted	FEV_1/FVC, %	TLC, % Predicted	D_{LCO}, % Predicted	Pao_2, mm of mercury	$PAo_2 - Pao_2$, mm of mercury	Shunt Fraction, %*	Contrast Echo
1	68	78	74	64	62	43	18	Intrapulmonary right-to-left shunt present
2	NA	NA	NA	NA	36	66.5	NA	Intrapulmonary right-to-left shunt present
3	64	67	86	57	43	66	18	Intrapulmonary right-to-left shunt present
4	59	77	NA	34†	NA‡	NA	20	NA

D_{LCO} = diffusing capacity of the lungs for carbon monoxide, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, NA = not available, $PAo_2 - Pao_2$ = alveolar-arterial oxygen gradient, TLC = total lung capacity

*Value is obtained with the patient sitting.
†Not corrected for the hemoglobin level.
‡Pao_2 = 45 mm of mercury while patient was receiving oxygen transtracheally at 6 liters/minute.

documented to resolve ranged from 1 to 8 months, when posttransplantation assessments were done.

Figure 2 depicts the change in the $PAO_2 - Pao_2$ gradient values before and after transplantation in all three patients while they were breathing room air. While patient 4 was receiving 6 liters of transtracheal oxygen before transplantation, the Pao_2 was 45 mm of mercury; after transplantation the $PAO_2 - Pao_2$ gradient was 29.7 mm of mercury. In the absence of demonstrable right-to-left shunting after liver transplantation to suggest persistent hepatopulmonary syndrome, persistent elevation of the $PAO_2 - Pao_2$ gradient was thought to indicate other causes of abnormal oxygenation, such as persistent ventilation/perfusion mismatching.

Discussion

The current study elicited the following findings:

- The prevalence of clinically suspected hepatopulmonary syndrome was 4% among this group of liver transplant recipients.
- The hepatopulmonary syndrome was uniformly reversible following liver transplantation in the four patients in whom it was detected in this series.
- The time to detected reversal of the hepatopulmonary syndrome was one to eight months in this series.

The estimated prevalence of the hepatopulmonary syndrome of 4% in the current series is lower than other available estimates, which range from 13% to 47%.[23,32] Specifically, a group of 40 liver transplant candidates were systematically screened for the hepatopulmonary syndrome.[32] The investigators noted that 13% (5 of 38) of these patients had echocardiographic evidence of intrapulmonary vascular dilatations, the hallmark of the syndrome. In another series, 53 liver transplant candidates were studied, and evidence of intrapulmonary right-to-left shunting was demonstrated in 25 (47%) by contrast-enhanced echocardiography.[23] That our prevalence estimate is lower than that of others probably reflects the dependence on the clinical recognition of the hepatopulmonary syndrome in the current series rather than systematic screening with contrast-enhanced echocardiography or radionuclide scans, as was undertaken in the two other series cited. Evidence of intrapulmonary right-to-left shunting by contrast-enhanced echocardiography has been shown in patients lacking clinical features of the hepatopulmonary syndrome such as orthodeoxia, platypnea, or both.[32] Furthermore, it has been observed that contrast-enhanced echocardiograms positive for right-to-left intrapulmonary shunting in 10% of cirrhotic patients with Pao_2 values exceeding 70 mm of mercury suggest a disparity between the anatomic evidence of right-to-left shunt and physiologic evidence of venous admixture.[32] Discordance was also reported recently between the results of contrast-enhanced echocardiography and physiologic shunt studies in 60 liver transplant candidates.[33] Of the 26 patients with discordant results (such as positive echocardiographic study for intrapulmonary right-to-left shunt but shunt less than 5%), 12 (20%) had positive contrast-enhanced echocardiograms but normal shunt studies and 14 (23%) had positive shunt studies but normal echocardiograms.

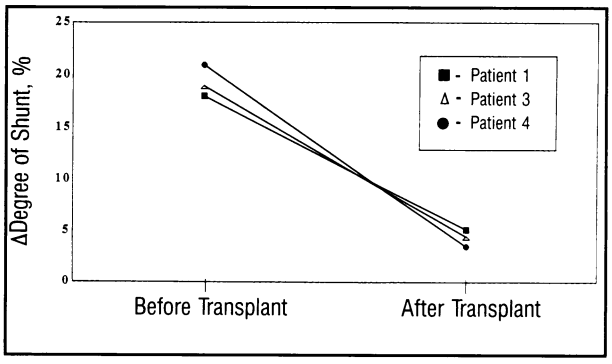

Figure 1.—The graph depicts the results of shunt fraction before and after liver transplantation in the 3 patients in whom both measurements were available. Shunt fractions decreased markedly in all 3 patients. The range of time between shunt assessments was 1 month in patient 1 to 8 months in patient 4.

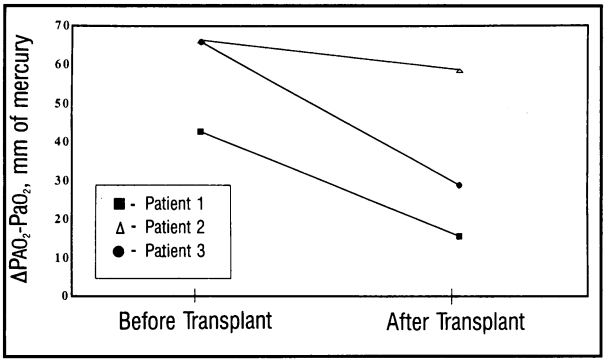

Figure 2.—The graph shows the results of the alveolar-arterial oxygen gradient ($P_{AO_2} - P_{aO_2}$) taken with the patient breathing room air in the 3 patients in whom both measurements were available. The mean $P_{AO_2} - P_{aO_2}$ decreased after liver transplantation from 58.1 to 33.4 mm of mercury, but remained abnormally elevated.

In the context that some persons may have evidence of intrapulmonary vascular dilatation with little impairment of gas exchange, we suspect that systematic screening of the 98 patients in this series would have detected additional patients whose hepatopulmonary syndrome was more clinically subtle than in the 4 patients reported here. To address this suspicion, current practice at the Cleveland Clinic Foundation is to evaluate all prospective liver transplantation candidates with two-dimensional surface contrast-enhanced echocardiography and shunt determinations done with the patient breathing 100% oxygen. Transesophageal echocardiography, which we have used to identify the site of intrapulmonary vascular dilatation by localizing contrast bubbles in specific pulmonary veins,[24] has not been performed routinely. Similarly, until the therapeutic relevance of distinguishing between a type 1 (diffuse "spiderlike" vessels) and a type 2 (discrete vascular changes) angiographic pattern is better understood, we have reserved the use of pulmonary angiography for standard indications—suspected pulmonary embolism or large arteriovenous malformations.

Our finding that the hepatopulmonary syndrome was universally reversible following liver transplantation in this series is also at odds with existing observations. Table 3 reviews the frequency with which intrapulmonary shunting caused by the hepatopulmonary syndrome lessened or reversed following liver transplantation in available series and indicates that 52% complete reversal and 43% partial abatement occurred.[8,10-19,32,34-40] Although some reports do demonstrate failure of the hepatopulmonary syndrome to resolve or to lessen at all following liver transplantation (Table 3), we suspect that "publication bias"[41] has inflated

TABLE 3.—*Review of Available Reports Regarding Reversal or Improvement of Intrapulmonary Shunt in Liver Disease*

Source	Patients, No.	Liver Disease	Transplanted, No.	Resolved Partial (P) vs Total (T), %
Silverman et al, 1968[34]	2	NS	0	T: 50 (after liver recovery in 1 pt)
Starzl et al, 1968[10]	3	NS	3	P: 100
Stanley and Woodgate, 1972[35]	1	Fascioliasis	0	T: 100 (after liver recovery)
Chen et al, 1984[36]	1	Alcoholic cirrhosis	0	T: 100 (after liver recovery)
Salem et al, 1989[37]	1	NS	0	P: 100 with somatostatin analogue
Shijo et al, 1989[38]	1	Cryptogenic cirrhosis	0	P: 100 after liver recovery
Eriksson et al, 1990[12]	6	Mixed	6	T: 83*; P: 17
Krowka et al, 1990[32]	1	Chronic active hepatitis	1	0
Mews et al, 1990[8]	1	Wilson's	1	0
Stoller et al, 1990[11]	1	Primary biliary cirrhosis	1	T: 100
Dimand et al, 1991[14]	3	Mixed; portal hypertension	3	P: 67; T: 33
Levin et al, 1991[13]	1	Extrahepatic biliary atresia	1	T: 100
McCloskey et al, 1991[17]	1	Cryptogenic cirrhosis	1	T: 100
Cadranel et al, 1992[39]	1	Nodular regenerative hyperplasia	0	T: 100 after medical therapy
LaBerge et al, 1992[15]	2	Cirrhosis due to extrahepatic biliary atresia	2	T: 100
Barry et al, 1993[20]	7	NS	7	T: 28; P: 72
Scott et al, 1993[16]	6	NS	6	P: 50; T: 50
Itasaka et al, 1993[18]	1	Cryptogenic cirrhosis	1	T: 100
Schwarzenberg et al, 1993[19]	1	α_1-Antitrypsin deficiency	1	T: 100
Shijo et al, 1993[40]	1	Macronodular cirrhosis	0	P: 100 (spontaneous improvement)
Total	42		32	Partial improvement: 43 Total improvement: 52

NS = not specified

*As determined by the alveolar-arterial oxygen gradient.

the prevalence of reported reversibility, especially because the concept that the hepatopulmonary syndrome can be reversed has gained recognition only over the past several years (since 1989). Because no large series evaluating the reversibility of hepatopulmonary syndrome after liver transplantation is available, case reports or small case series of patients with the hepatopulmonary syndrome failing to improve after liver transplantation seem less newsworthy and, therefore, less likely to be submitted or accepted for publication. To the extent that the 4 patients in this report with reversible hepatopulmonary syndrome represent only a fraction of all such patients among our 98 liver transplant recipients, we suspect that our data may overestimate the frequency with which the hepatopulmonary syndrome reverses after liver transplantation.

Finally, our observation that the hepatopulmonary syndrome resolved within eight months after liver transplantation is consistent with observations by others.[10-20] As presented in Table 4, some reports document improvement in the shunt fraction within days of liver transplantation, whereas others show more delayed resolution (2 to 14 months). Because none of the available series has done testing for the hepatopulmonary syndrome at frequent, predetermined intervals following transplantation, some of the splay in the observed time course of resolution may reflect managing physicians' decisions to defer postoperative testing for the syndrome until patients were beyond the immediate postoperative period. Also, in the absence of a specified posttransplantation protocol for retesting for the syndrome, clinicians are likely to reassess only when clinical improvement is evident enough to justify the inconvenience, expense, and morbidity of repeated testing. In patient 1 in the current series (whose case was reported previously[11]), the resolution of clinical features of the hepatopulmonary syndrome was evident within 37 days after liver transplantation (that is, by the resolution of digital clubbing and a reduction in shunt fraction), but was incomplete by the second postoperative day (based on the persistence of a positive contrast-enhanced echocardiogram at 34 hours).

Several shortcomings of the current study are evident. Like most available series, pretransplantation screening for the hepatopulmonary syndrome was not uniform in this series, so that underdetection of the syndrome is

TABLE 4.—*Time to Resolution of the Hepatopulmonary Syndrome Following Liver Transplantation in Available Series*

Source	Patients, No.	Age, yr	Disease	Pao_2, mm of mercury		Shunt, %		Time to Resolution
				Room Air	100% Oxygen	100% Oxygen*	^{99m}Tc†	
Starzl et al, 1968[10]	3	<20 mo	Mixed	85-88‡	NR	50	NR	Decreased shunt (5%-15%) immediately in 2 patients and after 10 days in the 3rd
Eriksson et al, 1990[12]	6	18-45	Mixed	78.8§	NR	4.3‖	NR	Follow-up 2-12 mo: 2 patients with shunt, 1 with normal Pao_2 within a few weeks
Stoller et al, 1990[11]	1	39	Primary biliary cirrhosis	62	290	18	NR	Normal shunt fraction (5.1%) at 37 days
Dimand et al, 1991[14]	3	13-53	Not specified	50.3§	289§	NR	Present	Decreased shunt and off supplemental O_2 at 3-4 mo
Levin et al, 1991[13]	1	11	Biliary atresia	44.8	NR	NR	Large	6 mo: resolution of shunt; 8 mo: improvement in O_2 saturation
McCloskey et al, 1991[17]	1	17	Cryptogenic cirrhosis	41	115	NR	30	9 mo: Pao_2 79 mm of mercury and 3% shunt
LaBerge et al, 1992[15]	2	12, 14	Biliary atresia	52§	233§	35	Present	Improved exercise tolerance at 3 mo, normal shunt study at 5 mo
Barry et al, 1993[20]	7	NR	Mixed	NR	NR	24.5	NR	Follow-up interval 3-18 mo: shunt fraction improved by 14% as a group
Itasaka et al, 1993[18]	1	13	Cryptogenic cirrhosis	42	417	52¶	48	Resolution of shunt at 165 days after transplantation
Schwarzenberg et al, 1993[19]	1	18	α_1-Antitrypsin deficiency	34	57	NR	Large	At 14 mo: Pao_2 116 mm of mercury and no shunt
Scott et al, 1993[16]	6	NR	Not specified	35-71#	350-460#	NR	12-19	3 patients: prompt resolution of shunts; 3 patients: long postoperative course, but shunt resolved

NR = not reported

*The values are the calculated shunt fraction with the patient breathing 100% oxygen, unless otherwise stated.
†Technetium Tc 99m-labeled macroaggregated albumin scan.
‡The numbers represent saturation values.
§The number is the mean value.
‖Multiple inert gas elimination technique was used.
¶By direct measurement of the shunt at cardiac catheterization.
#The numbers represent the range.

likely. Similarly, the timing of posttransplantation retesting for the hepatopulmonary syndrome was not uniform, so that our understanding of the frequency of reversal of the syndrome and of the time frame over which reversal occurs is incomplete. Finally, the small number of patients having the reversal of the hepatopulmonary syndrome in this and other series precludes a clear understanding of pretransplantation clinical features associated with the reversibility of the syndrome. Indeed, in the absence of a better understanding about predicting reversibility of the syndrome, a firm recommendation to do transplantation in all patients with the hepatopulmonary syndrome is not possible. Nonetheless, bolstered by the observation that the syndrome can reverse following liver transplantation, it is reasonable to consider this procedure for patients whose hepatopulmonary syndrome is the major debilitating feature[11] and who are otherwise deemed to be candidates for liver transplantation. To address the aforementioned shortcomings, we are currently prospectively evaluating liver transplantation candidates referred to our institution, in which patients are routinely assessed for the hepatopulmonary syndrome as part of their pretransplantation evaluation.

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